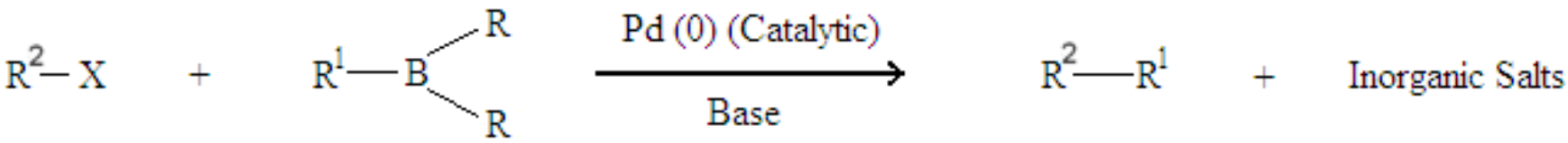
Suzuki Cross-Coupling

November 8 2008

Chem 4D03

The Overall Reaction

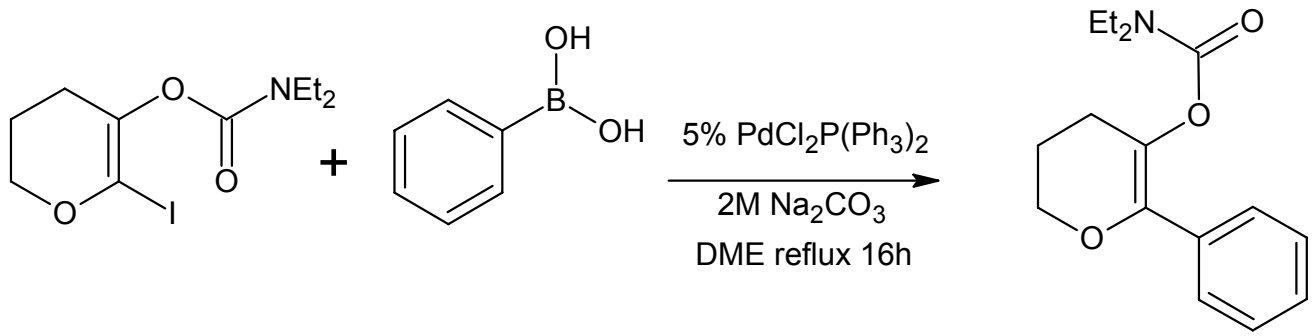
- Reported in 1979 by Akira Suzuki and N. Miyaura
- Commonly referred to as the Suzuki cross-coupling
- Palladium catalyzed cross-coupling between organoboron compounds and organic halides leading to the formation of carbon-carbon bonds.



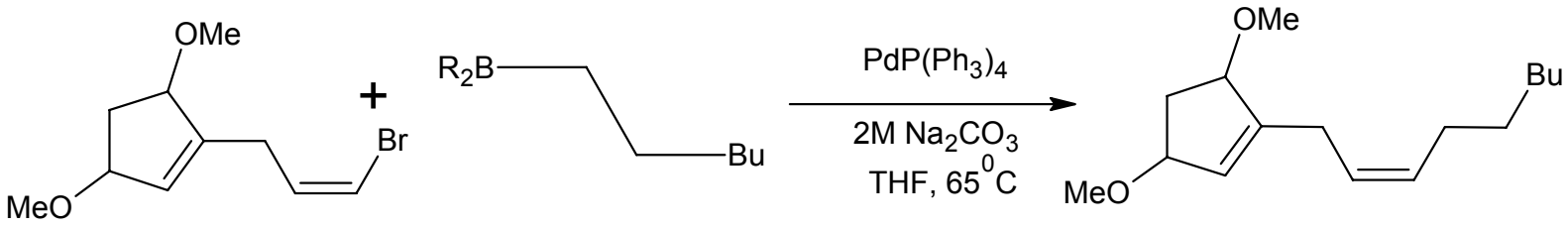
R^1= alkyl, allyl, alkenyl, alkynyl, aryl; R = alkyl, OH, O-alkyl; R^2= alkenyl, aryl, alkyl; X = Cl, Br, I, OTf
Base = Sodium Carbonate, Sodium Hydroxide, M (O-alkyl), Potassium phosphate tribasic

(Kurti L. and Czako B., 2005)

The Overall Reaction Cont'd

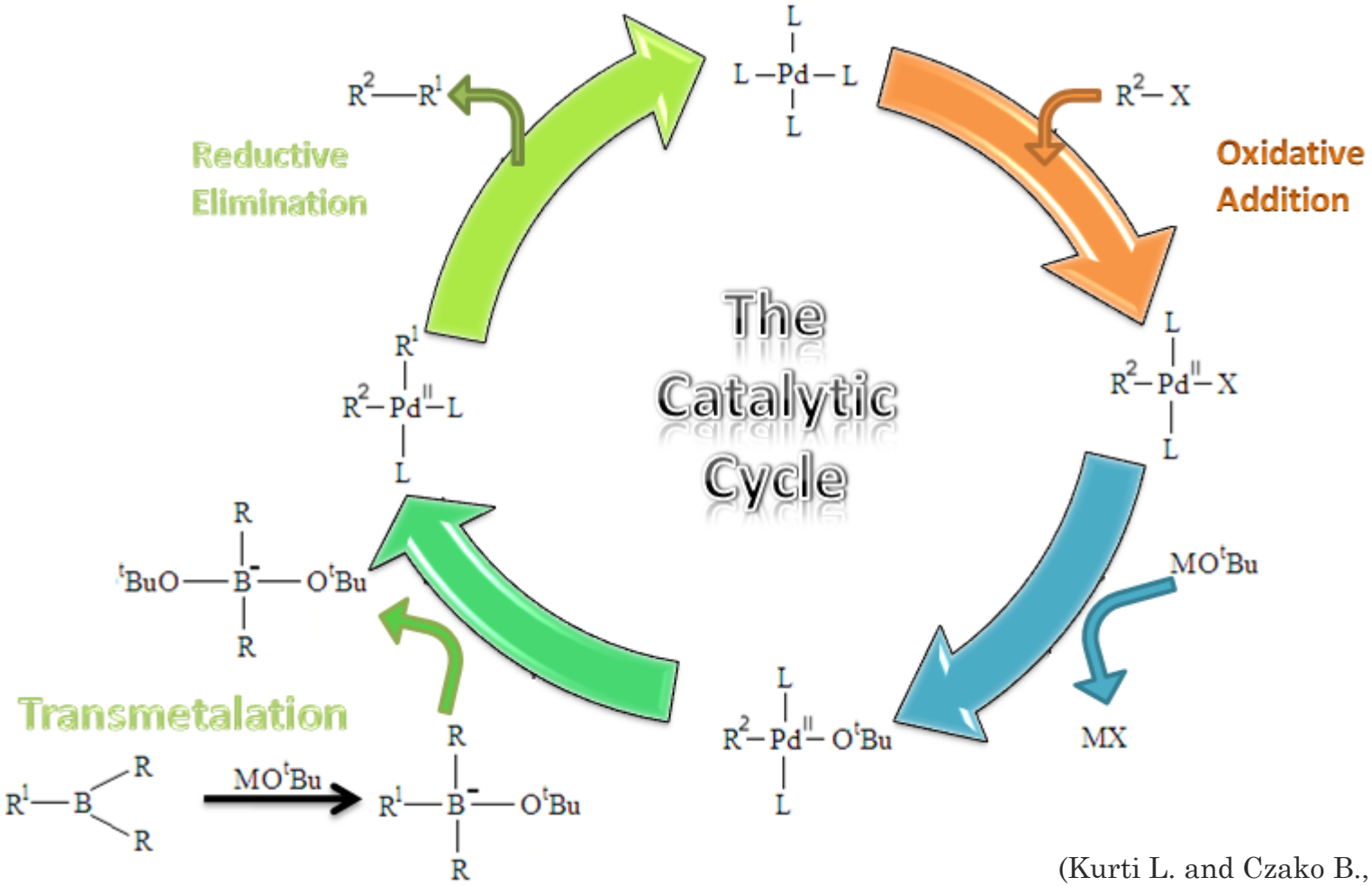


(Bower et al., 1998)



(Thompson et al., 1998)

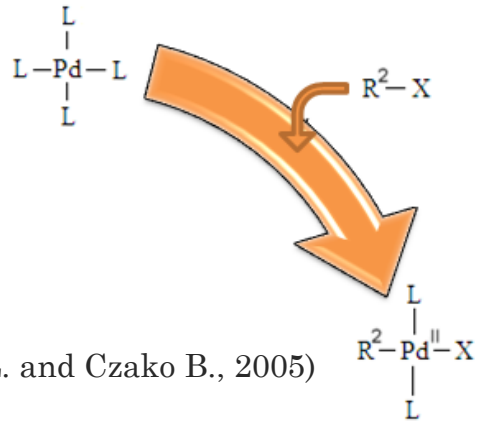
The Reaction Mechanism



(Kurti L. and Czako B., 2005)

Oxidative Addition

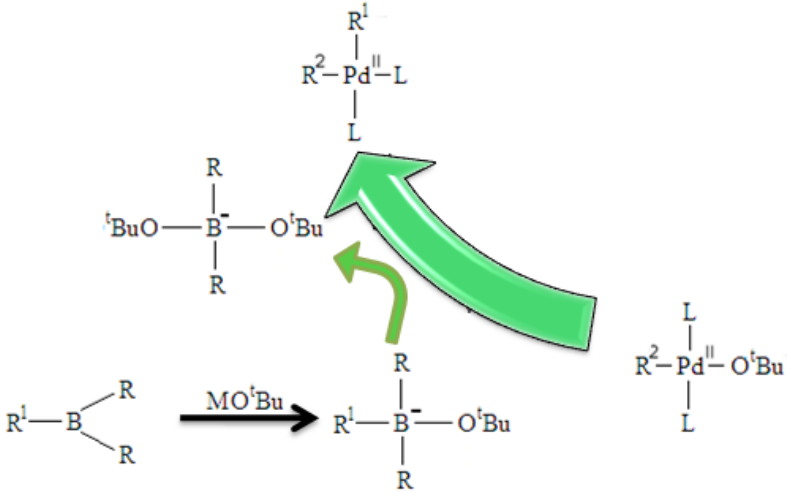
- The rate determining step of the catalytic cycle
- Couples the palladium catalyst to the alkyl halide which gives rise to the organopalladium complex
- The complex is initially in the cis conformation but isomerizes to the trans conformation
- Stereochemistry with vinyl halides are retained but inversion of stereochemistry occurs with allylic or benzylic halides

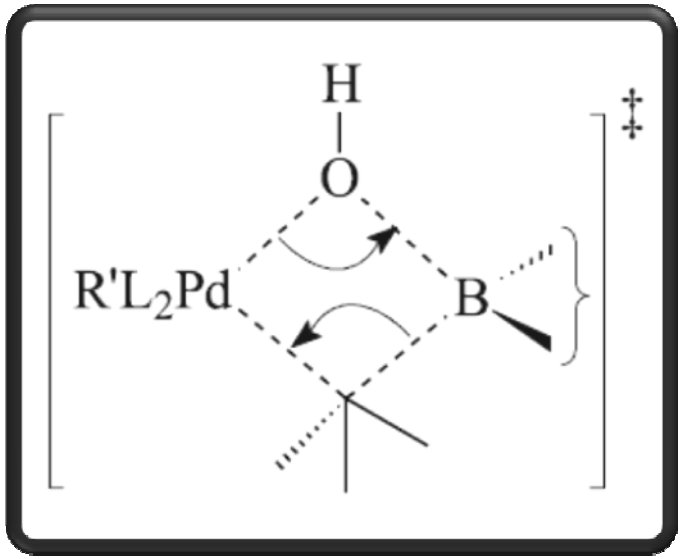


(Kurti L. and Czako B., 2005)

Transmetalation

- The role of base is to activate the boron-containing reagent, and also facilitate the formation of R1Pd-OR from R1Pd-X.
- Reaction does not occur in the absence of base.
- Exact mechanism is unclear.

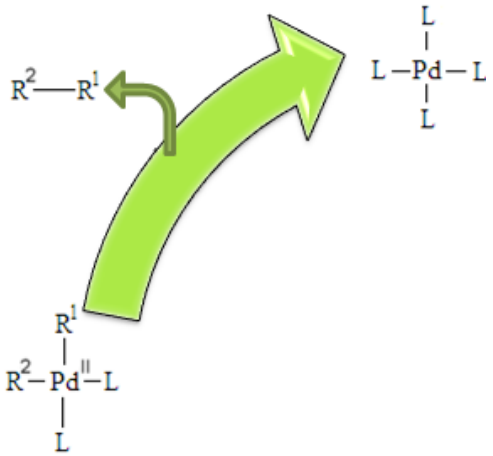




(Figure modified from Dhillon 2007)

Reductive Elimination

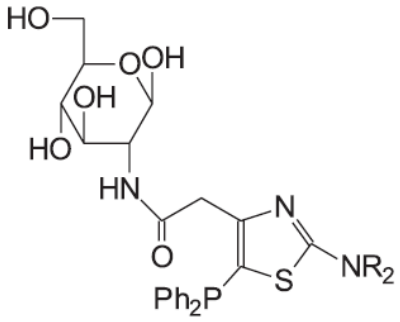
- This final step gives the desired product and it also regenerates the palladium catalyst so that it can participate again in the catalytic cycle (ie. making more products).
- Require the complex to revert back to the cis conformation before reductive elimination can occur

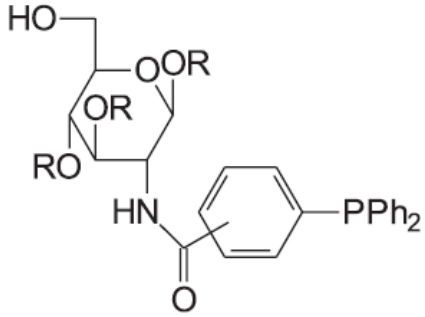


(Kurti L. and Czako B., 2005)

The Catalyst

- Typically, triphenylphosphine is the ligand used to activate the palladium
- Can also be ligandless such as Pd/C
  - Easier to handle (other ligands may be air-sensitive)
  - Remove by simple filtration (recover, purify, and reuse)
- Other types of ligand
  - Carbohydrate derivatives – increase solubility of the metal-ligand complex

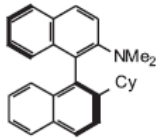




Figures modified from
(Franzén and Xu 2005)

Variations

- Asymmetrical Suzuki cross coupling
  - Employ chiral binaphthalene derivatives

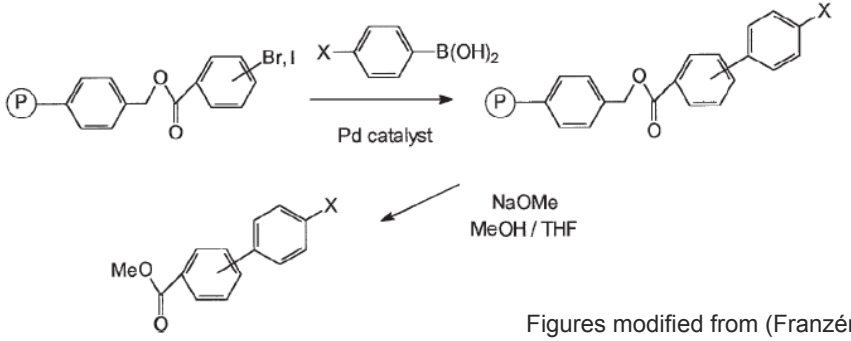


= Ligand

(*S*)(+)

Figure modified from (Franzén and Xu 2005)

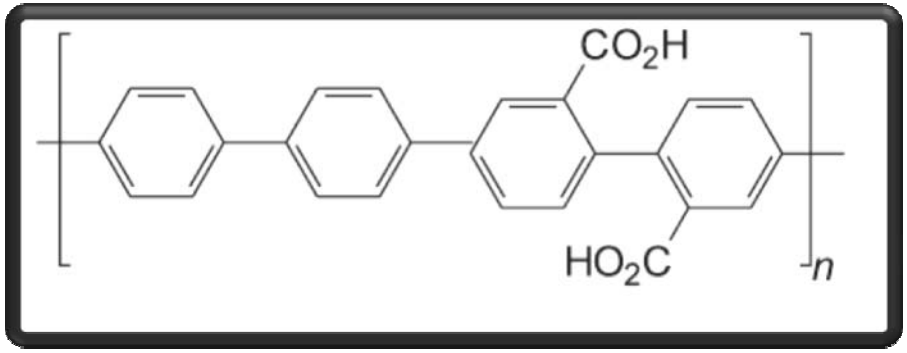
- Solid-phase synthesis (Frenette and Friesen 1994)

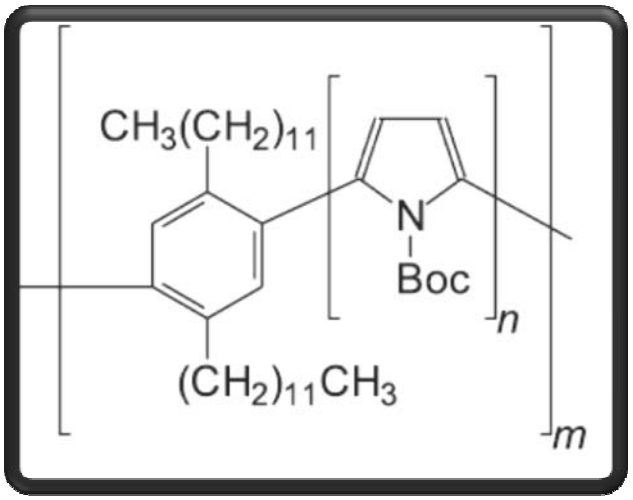


Figures modified from (Franzén 2000)

Variations Cont'd

- Preparation of Polymers
- Possibility of synthesizing chiral polymers in solid phase!



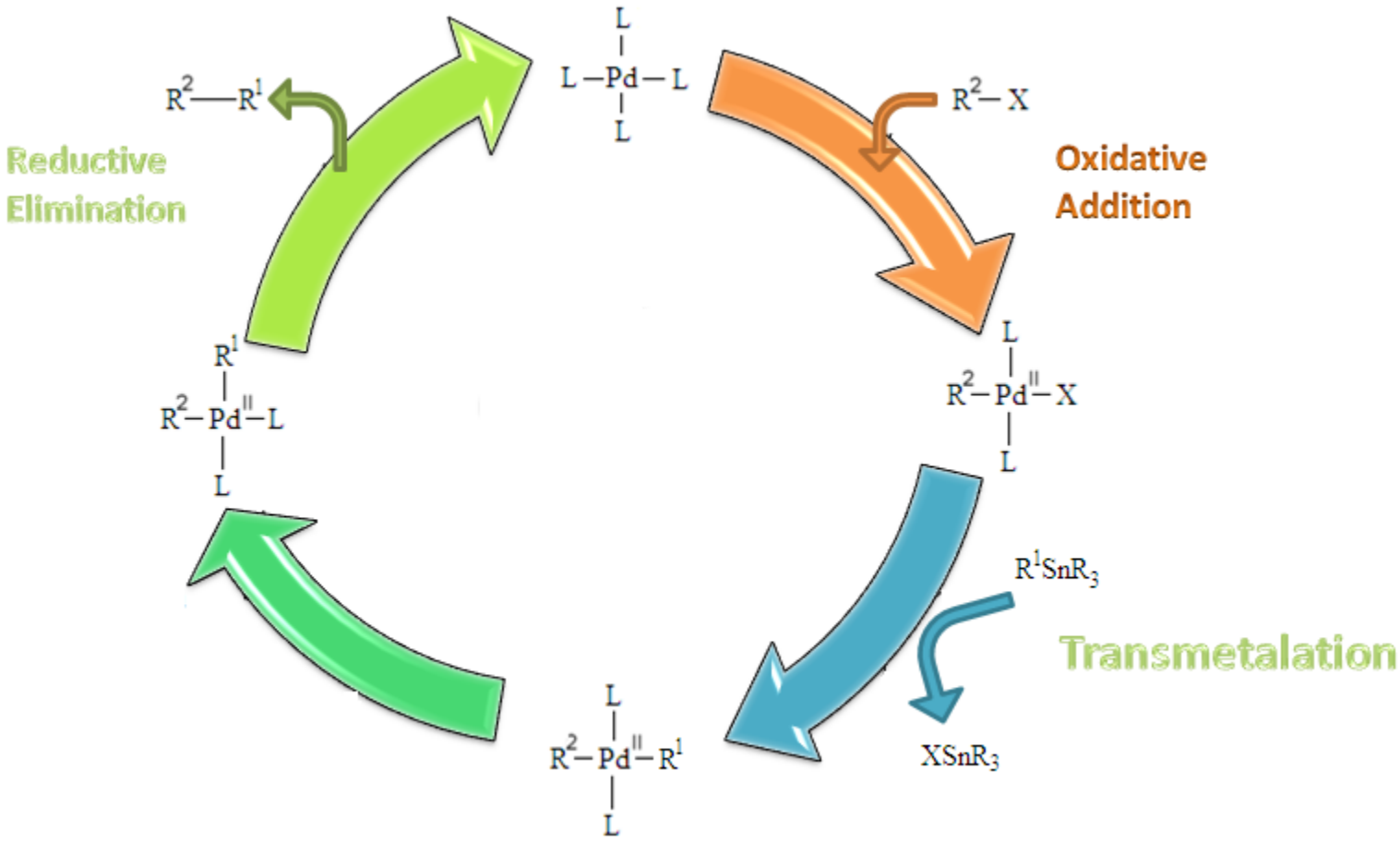


Figures modified from
(Franzén and Xu 2005)

Advantages

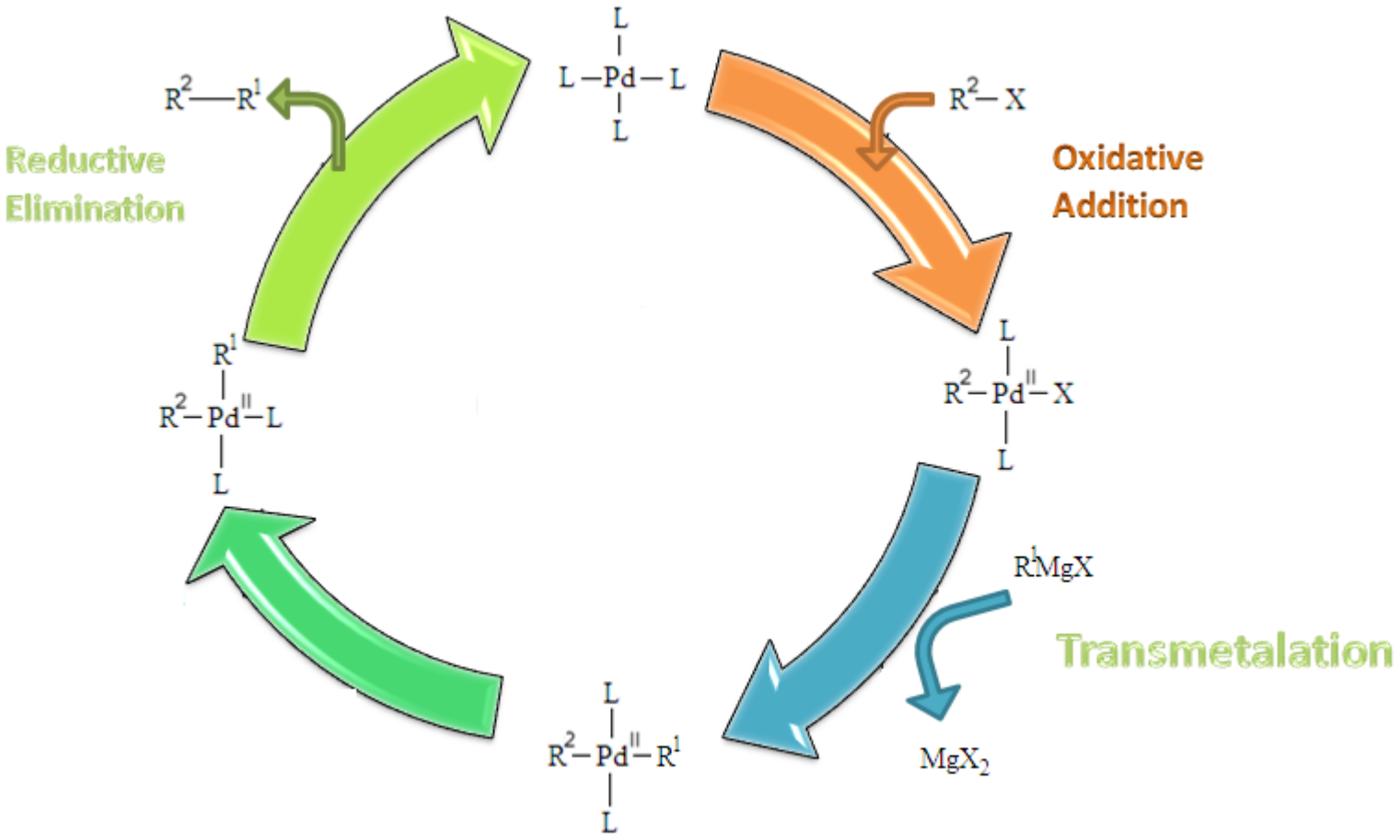
- Mild Reaction Conditions
- Availability of common boronic acids
- Inorganic by-products are easily removed from reaction mixture.
- Stereoselective
- Less toxic than other competitive methods, (ie. Boronic acids are environmentally safer and less toxic than organostannanes)
- Reaction will take place in the presence of other functional groups (ie. protecting group is not always necessary)
- Relatively cheap reagents, easy to prepare, and GREEN!

Stille Cross Coupling



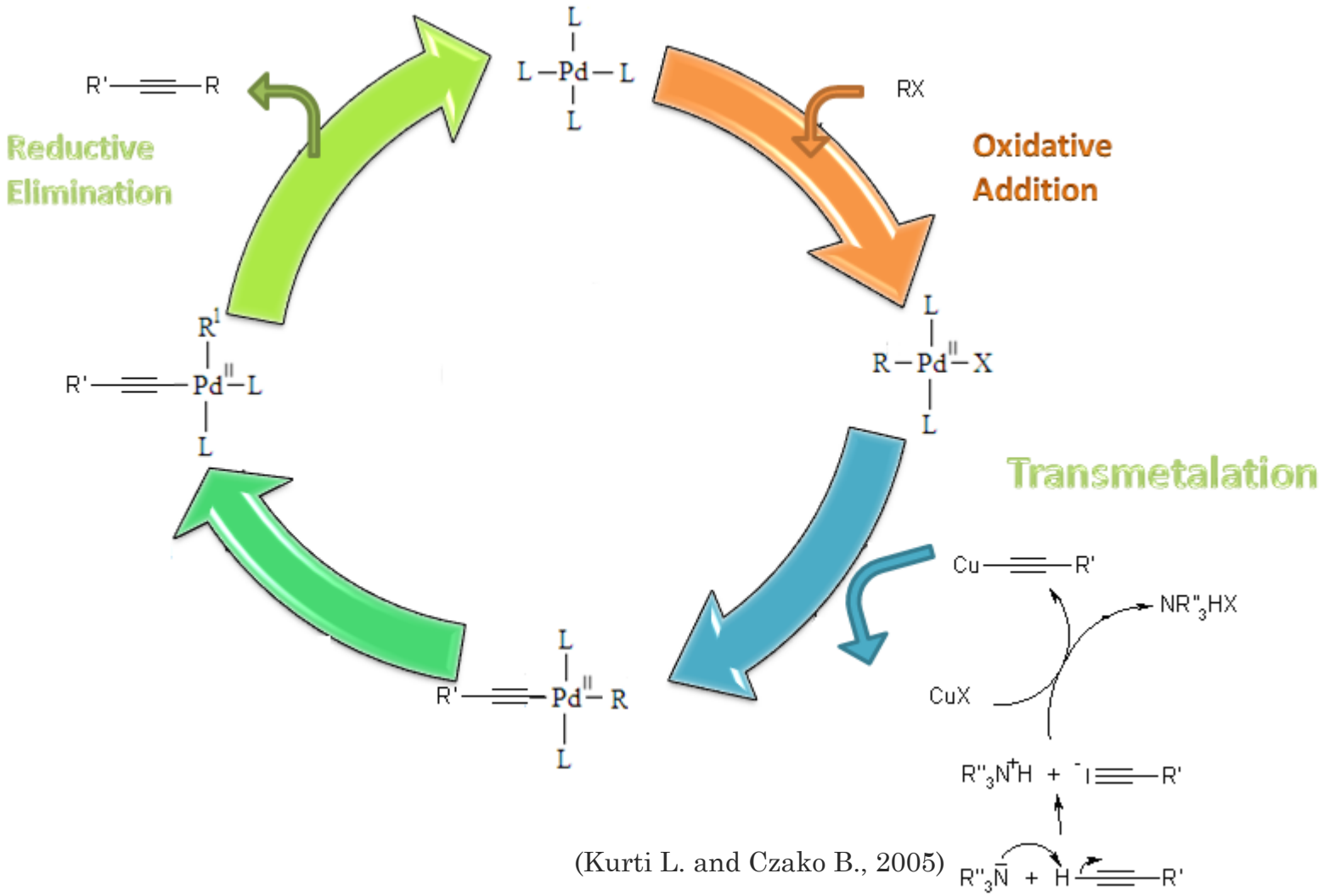
(Kurti L. and Czako B., 2005)

Kumada Coupling



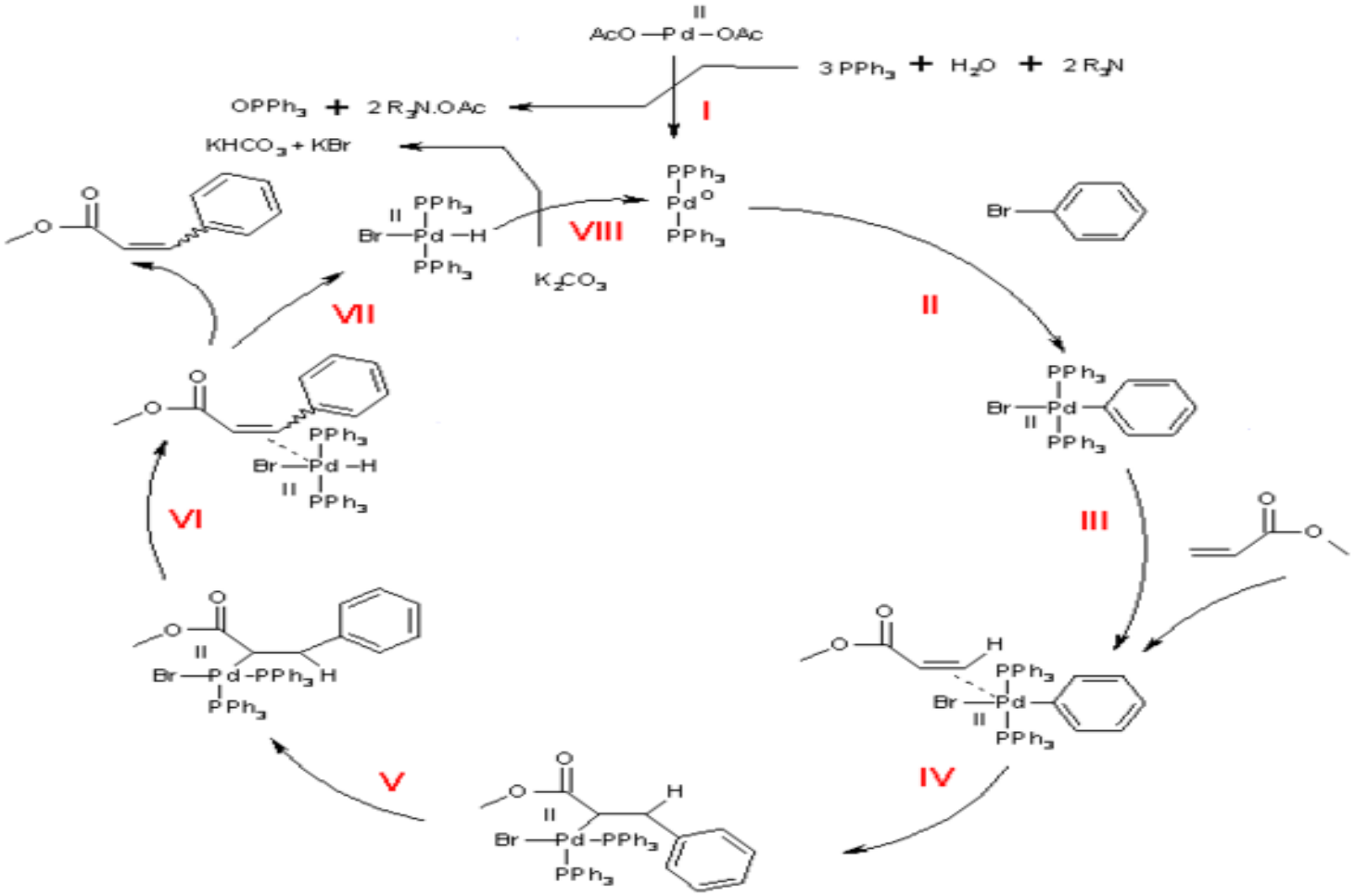
(Kurti L. and Czako B., 2005)

Sonogashira Coupling



(Kurti L. and Czako B., 2005)

The Heck Reaction



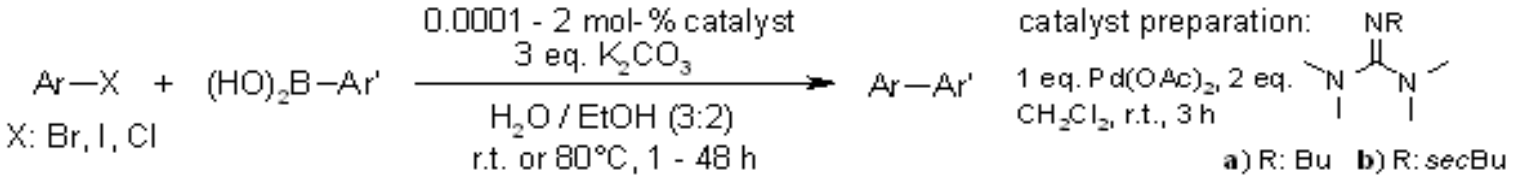
(Clayden J., 2001)

Disadvantages

- Aryl chlorides react sluggishly
- sp^3-hybridized alkyl halides sometimes show no reactivity
- Beta hydride elimination is observed with alkyl bromides that possess beta hydrogen atoms
- In the absence of base, multiple side reactions are possible

Aryl Chlorides

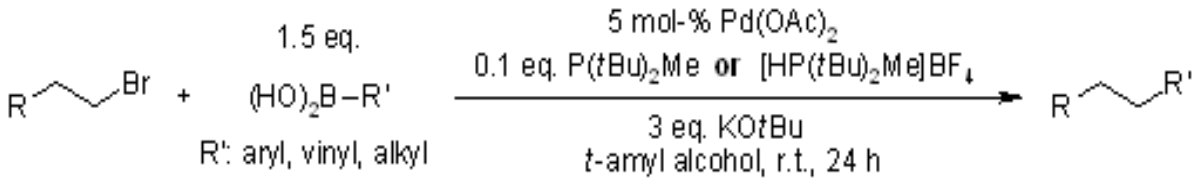
- Aryl chlorides react sluggishly when using phosphine ligands with the Pd(0) catalyst. Often requires heat.
- But using the phosphine-free $Pd(OAc)_2$/Guanidine catalyst solves this problem.
- The reaction occurs in room temperature.
- The reaction is phosphine-free.



(Li et al., 2007)

Catalysts for sp^3-hybridized Alkyl Halides

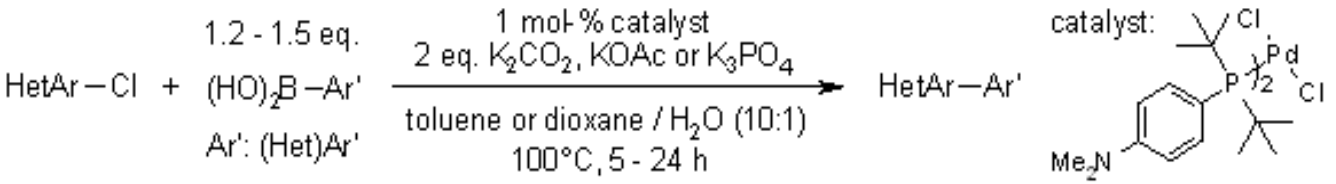
- Using $Pd(Ph_3)_4$ the cross-coupling of boronic acids with unactivated alkyl electrophiles (alkyl halide) is very hard to achieve.
- The alkyl halide doesn't easily oxidatively add to Pd(0).
- $Pd(P(t\text{-}Bu)_2Me$ and the alkyl halide undergo oxidative addition in mild conditions (r.t.) and the resulting adduct is stable toward b-hydrogen elimination.
- $Pd(P(t\text{-}Bu)_2Me$ is more sterically favoured than $Pd(PPh_3)_4$



(Kirchhoff et al. 2002)

Additional Catalysts

- $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalyzes Suzuki coupling reactions of a variety of heteroatom-substituted heteroaryl chlorides with a diverse range of aryl/heteroaryl boronic acids



(Guram et al., 2007)

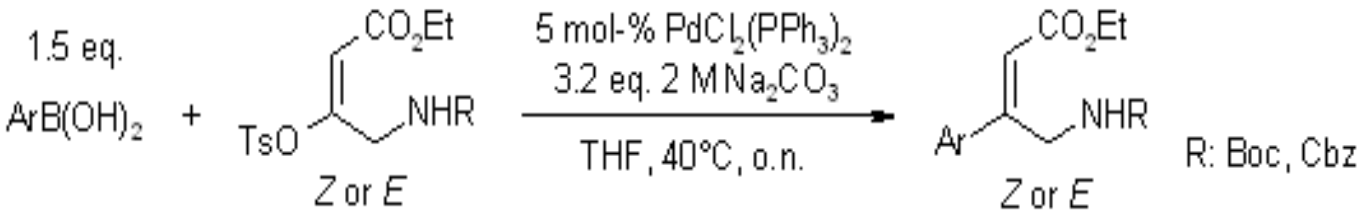
Additional Catalysts

- When using $Pd(PPh_3)_4$ as catalyst, the heteroatom on the heteroaryl chloride can bind to the metal centre and deactivate the catalyst.
- The electron-rich nature of phosphine ligands, $\{PR_2(Ph\text{-}R')\}_2$, promotes the oxidative addition of the C-Cl bond, while the steric properties of the phosphine ligands are particularly favorable for the coupling reactions of heteroatom-containing substrates.

(Guram et al., 2007)

Variations on the Reactants

- Enol tosylates are stable, crystalline compounds that undergo smooth and effective Suzuki coupling with a variety of aryl boronic acids.



(Baxter et al. 2005)

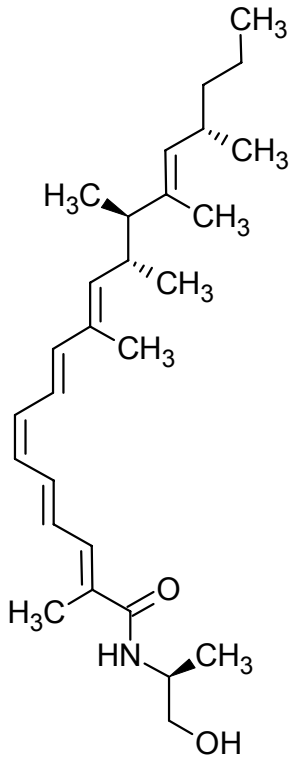
Variations on Reagents Cont'd

- The enol tosylate was used instead of the enol triflate because in the reaction conditions, the triflate decomposes resulting in a low yield of the product.
- The nonaflate equivalents ($CF_3CF_2CF_2CF_2SO_3^-$) could have been used the process involves a transmetalation step or requires Stille coupling conditions, which were avoided.

(Baxter et al. 2005)

Synthetic Applications

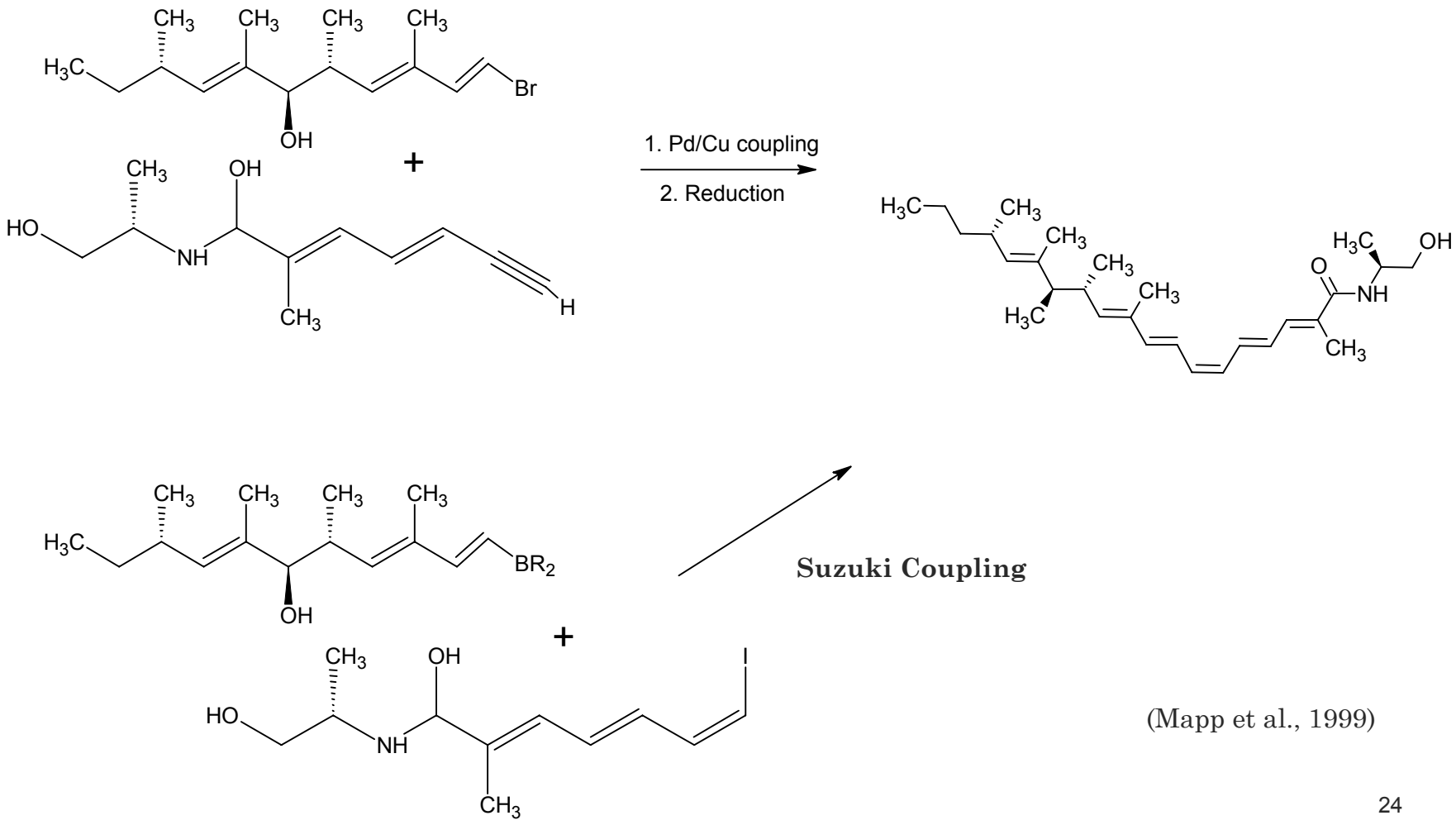
- The last step in the synthesis of Myxalamide A
- Polyene antibiotic
- Isolated from the bacterium Myxococcus xanthus
- Observed to have antibiotic and antifungal activity



Myxalamide A

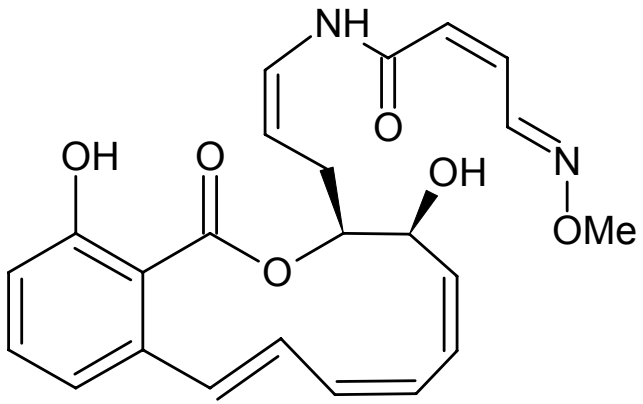
(Mapp et al., 1999)

Myxalamide A



(Mapp et al., 1999)

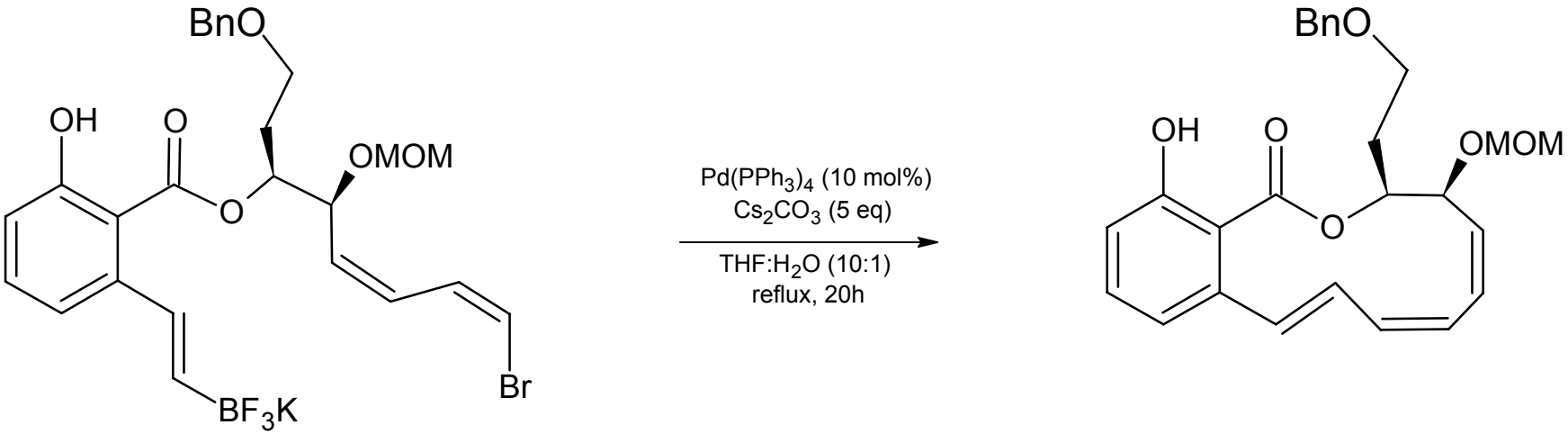
Synthesis of Oximidine II



(Molander et al., 2004)

- Oximidines were first isolated in 1999 from Pseudomonas sp. Q52002.
- Highly biologically active
- Affect the cell cycle at the G1 Phase
- Coupling used in the synthesis of the macro-cyclic ring

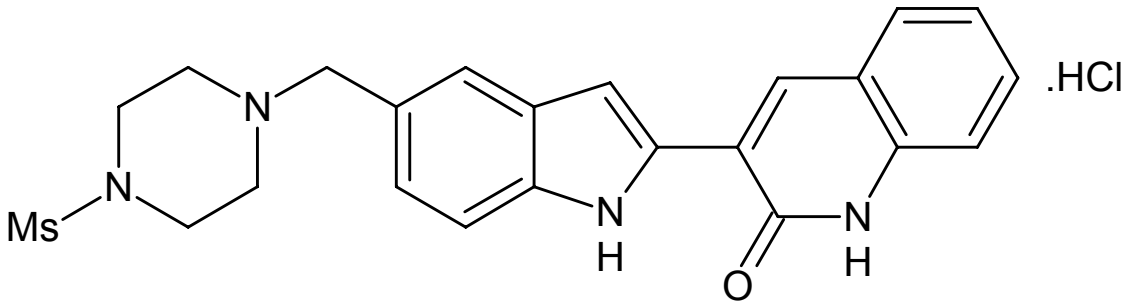
Intermediates in Oximidine II Synthesis



(Molander et al., 2004)

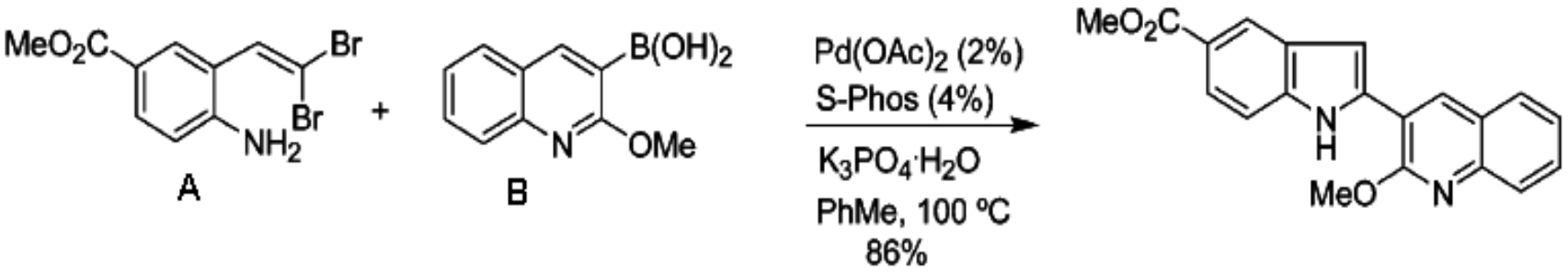
Synthesis of KDR Kinase Inhibitor

- KDR kinase inhibitors, inhibit the activity of specific tyrosine kinase enzymes in the body.
- Tyrosine kinases catalyze the phosphorylation of –OH groups on tyrosine residues.
- The pyrrol ring is the group binds to the active site inhibiting the enzyme while bound.



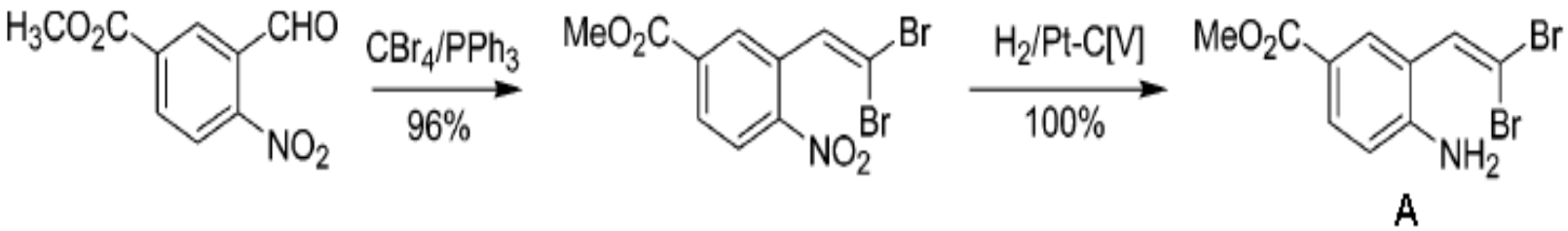
(Fang et al., 2006)

Key Step in KDR Kinase Inhibitor Synthesis



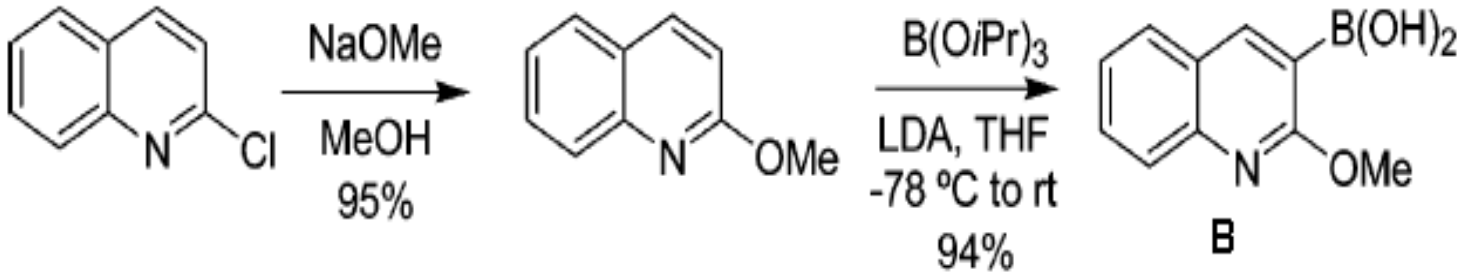
(Fang et al., 2006)

Synthesis of Compound “A”



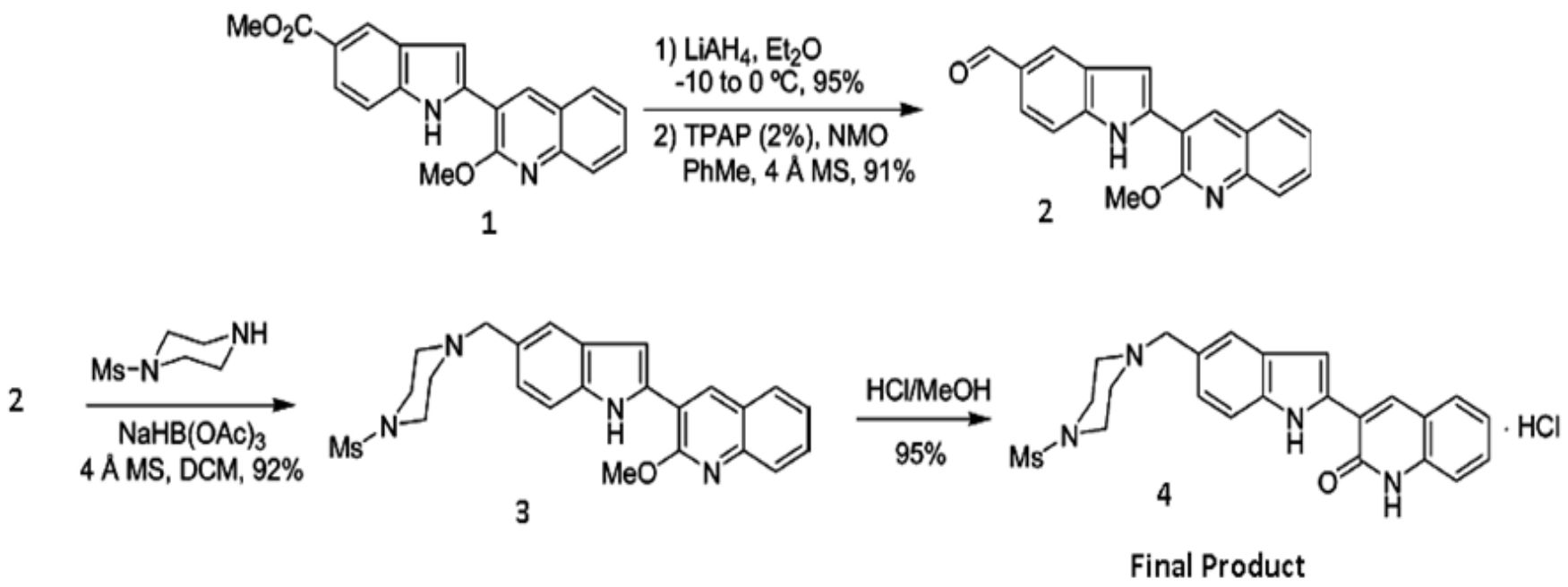
(Fang et al., 2006)

Synthesis of Compound “B”



(Fang et al., 2006)

Final Steps in Synthesis



(Fang et al., 2006)

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    S. Li, Y. Lin, J. Cao, S. Zhang, *J. Org. Chem.*, **2007**, *72*, 4067-4072.

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11. Yuan-Qing Fang, Robert Karisch, and Mark Lautens; Efficient Syntheses of KDR Kinase Inhibitors Using a Pd-Catalyzed Tandem C-N/Suzuki Coupling as the Key StepSyntheses of KDR Kinase Inhibitors, DaVenport Chemistry Laboratories, Department of Chemistry, University of Toronto: 2006